70. (New) The mutant human TSH heterodimer of Claim 69, wherein the at last one amino acid substitution is selected from the group consisting of βI58R and βE63R.

71. (New) The mutant TSH heterodimer of Claim 69, comprising a mutant human α subunit and a mutant human TSH β mutant subunit, wherein the mutant human TSH β subunit comprises at least one amino acid substitution in amino acid residues selected from among positions 58-68 of the amino acid sequence of human TSH β subunit as depicted in Figure 2 (SEQ ID NO:2).

B1

72. (New) The mutant TSH heterodimer of Claim 69, which is a mutant of a human TSH heterodimer.

73. (New) The mutant TSH heterodimer of Claim 69, wherein the hormonal half life in circulation in vivo of the mutant TSH heterodimer is greater than the wild type TSH.

74. (New) A diagnostic composition comprising an amount of the TSH analog of Claim 69 sufficient to stimulate iodine uptake by thyroid cancer cells; and a pharmaceutically acceptable carrier.--

REMARKS

Claims 69-74 are added. After entry of the above, Claims 27-31, 39, 62, and 67-74 remain pending in this application. Claims 27, 28 and 69 are the only independent claims. Support for the claims added may be found in Claim 28 and throughout the Specification.

No new matter is incorporated by this Amendment.

Rejection based on 35 U.S.C. § 103(a)

Claims 27-31, 39, 62, 67, and 68 are rejected under 35 U.S.C. § 103(a) as allegedly rendered unpatentable based on Szkudlinski, et al. ("Engineering Human Glycoprotein Hormone

Superactive Analogues," Nature Biotechnology,14, 1257-1263 (1996)) combined with Boime (U.S. Patent No. 5,585,345). See point 5 of the Official Action.

Applicants respectfully traverse.

As the Office action correctly indicates, Szkudlinski, et al. teaches engineering of the human glycoprotein hormones of thyroid stimulating hormone (TSH), chorionic gonadotropin (CG), luteinizing hormone (LH), and follicle stimulating hormone (FSH). However, the Office Action does not indicate that Szkudlinski, et al. is limited to teaching amino acid substitutions within the α and β subunits. There is no actual teaching or suggestion of any specific modifications to the hormone protein molecules outside the substitutions of amino acids along the sequence of the α and/or β subunits.

Szkudlinski, et al. is a research article that is noteworthy for demonstrating an effect on glycoprotein activity by substitutions in non-conserved regions between human TSH and bovine TSH. However, the article does not teach or suggest modifications to the TSH other than what is expressly stated or demonstrated. The Office Action cites Column 1, page 1257, at the end of the first paragraph, as purportedly providing some suggestion to make modifications to the subject matter glycoproteins beyond the substitutions in the mutants actually disclosed. But the teaching at this citation does not support this contention. It merely discusses the resulting effects on glycoprotein functional activity, *in vitro* and *in vivo*, based on the substitutions that are actually demonstrated. The cited statement from the article states:

> "[p]revious structure-function studies of glycoprotein hormones resulted in the "engineering" of long-acting analogues of glycoprotein hormones with a prolonged plasma half-life and increased in vivo bioactivity. However, there have been no reports of human glycoprotein hormone analogues that show a major increase in both in vitro and in vivo bioactivity."

This recitation in no ways suggests any specific, or general, modification to the glycoprotein structure other than the amino acid substitutions within the α and β subunits. The passage merely

discusses the data that was generated with respect to both *in vivo* and *in vitro* testing.

By way of contrast to how this teaching is characterized in the Office Action, Szkudlinski, et al., actually only teaches substitutions of amino acids along specific sites of the sequences forming the α and β subunits of the glycoproteins. Therefore, Szkudlinski, et al. does not teach or suggest any modifications beyond these site substitutions that occur within non-conserved regions in the α and β subunits of the glycoproteins, and by implication teaches away from combining this teaching with another hypothetical disclosure directed to other types of protein modifications.

Applicants have overcome a problem identified in the art for further modifications to TSH beyond mere substitution within the non-conserved regions of the α and β subunits of the TSH glycoprotein. In any event, Szkudlinski, et al. fails to teach or suggest a mutant TSH heterodimer comprising a TSH β subunit joined via a peptide bond at its carboxyl terminus to the amino terminus of the carboxyl terminal extension peptide (CTEP) of human chorionic gonadotropin as is required in all the claims.

With respect to newly added Claims 69-74, Applicants point out that, in addition to how Szkudlinski, et al. does not support the rejection addressed above, the reference also fails to teach or suggest a mutant TSH heterodimer wherein at least one amino acid substitution is in amino acid residues selected from among positions 58-68 of the amino acid sequence of the TSH β subunit as depicted in Figure 2 (SEQ ID NO:2).

In fact, Szkudlinski, et al., by implication, teaches away from any substitutions in the 58-68 region of the TSH β subunit. At page 1258, column 2, lines 10-14, Szkudlinski, et al. notes that the only substitution made on the TSH β subunit is limited to the 69 position. This is because the non-conserved regions of TSH in Szkudlinski, et al. were identified from between human TSH and bovine TSH, and the reference is directed making substitutions in only these

non-conserved regions. The reference implies that substitutions other than at the 69 position will have no effect upon bioactivity. As stated in the article, there are no other substantial differences between the human and bovine TSH β subunit, so any other substitutions within TSH β subunit as analyzed in Szkudlinski, et al. would not be expected to impact biological activity as only site 69 on the β-subunit presented a substantially non-conserved site between human and bovine TSH. Accordingly, Szkudlinski, et al. implicitly teaches away from any substitutions from among positions 58-68 of the amino acid sequence of TSH β subunit as required in Claim 69.

Boime fails to cure the deficiencies of Szkudlinski, et al. More particularly, although the Office Action looks to Boime to cure the deficiency in Szkudlinski, et al. with respect to having a CTP modification to TSH, Boime simply does not teach or adequately suggest a mutant TSH heterodimer comprising a TSH β subunit joined via a peptide bond at its carboxyl terminus to the amino terminus of the carboxyl terminal extension peptide of human chorionic gonadotropin.

Instead, Boime teaches multiple dissimilar ways to modify the different species of glycoprotein. But it does not teach a mutant TSH heterodimer comprising a TSH β subunit joined via a peptide bond at its carboxyl terminus to the amino terminus of the carboxyl terminal extension peptide (CTP) of human chorionic gonadotropin (CG).

Although Boime does teach a similar modification to follicle stimulating hormone (FSH) and luteinizing hormone (LH), it makes no mention of this modification to TSH. Also, there is no explanation of the underlying mechanism why the modification demonstrated for FSH and LH would have a similar effect on the biological activity of TSH. Furthermore, as TSH and FSH, or LH are active through different receptors, there is reason to doubt there would be a similar effect on TSH based upon a reading of Boime.

Applicants do note the general averment noted in the Office Action from Boime regarding appending the CTP of the CG to other proteins. The patent states with regard to the Carboxy Terminal Peptide Modification of other Peptide Hormones:

> As described above, the carboxy terminal portion of the CG beta subunit, or a variant of this carboxy terminal peptide, has significant effect on the clearance of CG, FSH and LH. This extension at the carboxy terminus has similar effects on the clearance of other hormones and protein-based pharmaceuticals in general.

However, this simply does not reach a teaching of a mutant TSH heterodimer comprising a TSH β subunit joined via a peptide bond at its carboxyl terminus to the amino terminus of the carboxyl terminal extension peptide of human chorionic gonadotropin. Applicants courteously note that the claimed invention is a molecule and that the effect to biological activity of modifications on a molecule are unpredictable. Furthermore, there is no specific teaching regarding TSH in Boime to cure the deficiency of Szkudlinski, et al. There is no teaching in Boime that would provide one of ordinary skill in the art motivation or direction to modify the mutant TSH of Szkudlinski, et al. There is no teaching in Boime of modifying either mutant or wild-type TSH with the CTP of CG. Therefore, the combination of Szkudlinski, et al. and Boime is not adequate to meet the claims as they do not adequately teach or suggest, alone or in combination, all the limitations in the claims.

There is another point regarding Boime and the modification of FSH, LH, and the inadequate general averment regarding modifying hormones or proteins in general with the CTP of CG. Boime merely suggests this will extend the *in vivo* activity of such modified moieties. As Boime states in the citation above, "this extension at the carboxy terminus has similar effects on the clearance of other hormones and protein-based pharmaceuticals in general." This does not identify the extent of the *in vivo* effect and simply does not contemplate the effect, if any, on *in vitro* activity. In addition, the data in Szkudlinski, et al., although directed to both the *in vitro*

irrelevant

and *in vivo* effect of single-site substitutions within the α and β subunits of the glycoproteins, is completely silent on the effect of appending the CTP of CG to any moiety.

Assuming *in arguendo*, that the combination of Szkudlinski, et al. and Boime were to complete a *prima facie* showing in obviousness, there is sufficient data in Applicants' specification that would rebut any such hypothetical *prima facie* showing. The data in Applicants' specification summarized in Figure 5 shows a higher bioactivity in cAMP production only 4K for an α-substituted TSH that is modified with the carboxy terminal moiety, than simply an α-substituted TSH heterodimer. Neither Szkudlinski, et al. or Boime contemplate this type of increase to *in vitro* activity based upon appending the CTP of CG to a mutant TSH heterodimer. As Applicants' specification states at page 42, lines 10-12: "It was surprising that the inclusion of CTEP, which is expected to prolong the in vivo half life of the α4K/β-CTEP heterodimer, also increased its in vitro activity a further 3-4 fold over that of a α4K/wild type β heterodimer." Accordingly, Applicants' invention demonstrates a surprising and unexpected improvement in the *in vitro* activity of mutant TSH based on the further modification to append the CTP of CG and would rebut any *prima facie* showing of non-obviousness.

It is respectfully submitted that the Official Action has failed to establish that the claimed invention is *prima facie* obvious. In addition, it is submitted that any such *prima facie* showing would be rebutted by the showing in the specification. Accordingly, reconsideration and withdrawal of all the rejection is respectfully requested.

Rejection based on Obviousness-Type Double Patenting

Claims 27-31, 39, 62, 67, and 68 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly rendered unpatentable based on Claims 1-43 and

47-57 of U.S. Patent No. 6,361,922 combined with Boime (U.S. Patent No. 5,585,345). See point 3 of the Official Action.

Applicants respectfully traverse.

As an initial matter, Applicants courteously point out that the claims of the '922 patent are not commensurate in scope with all the possible combinations of single-site substitutions contemplated by Applicants' claims under rejection.

In addition, Boime fails to cure the remaining deficiencies of the '922 patent claims for the same reasons it fails to cure the deficiencies of Szkudlinski, et al. as noted in the obviousness rejection addressed above.

Accordingly, reconsideration and withdrawal of all the obviousness-type double patenting rejection is respectfully requested.

CONCLUSION

All rejections having been addressed by the present amendments and response. Applicants submit that the present case is in condition for allowance and respectfully request early notice to that effect. If any issues remain to be addressed in this matter which might be resolved by discussion, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number indicated below.

Respectfully submitted,

PIPER RUDNICK LLP

CHRIS RAIMUND
REG. NO. 47,258

FOR Steven B. Kelber
Registration No. 30,073
Attorney of Record

Patrick R. Delaney
Registration No. 45,338

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. (202) 861-3900
Facsimile No. (202) 223-2085